



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(21) International Application Number:</b> PCT/GB97/02576<br><b>(22) International Filing Date:</b> 23 September 1997 (23.09.97)<br><b>(30) Priority Data:</b><br>60/028,212      1 October 1996 (01.10.96)      US<br><b>(71) Applicants (for all designated States except US):</b> BION-UMERIK PHARMACEUTICALS, INC. [US/US]; Suite 1250, 8122 Datapoint Drive, San Antonio, TX 78229 (US). LUCAS, Brian, Ronald [GB/GB]; Lucas & Co., 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB).<br><b>(72) Inventor; and</b><br><b>(75) Inventor/Applicant (for US only):</b> HARIDAS, Kochat [IN/US]; 2507 Steepleway, San Antonio, TX 78248 (US).<br><b>(74) Agent:</b> LUCAS & CO.; 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB).  |           | <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> PROCESS FOR PRODUCING MERCAPTOALKANESULFONATES AND PHOSPHONATES AND DERIVATIVES THEREOF  |           |   |
| <b>(57) Abstract</b><br><br><p>A two step single-pot process for producing dimesna (<math>\text{NaSO}_3-(\text{CH}_2)_2-\text{S}-\text{S}-(\text{CH}_2)_2-\text{SO}_3\text{Na}</math>) begins by reacting an <math>\omega</math>-alkenesulfonate, with a sulfide such as NaSH to yield mesna (<math>\text{HS}-(\text{CH}_2)_2-\text{SO}_3\text{Na}</math>). (This can be isolated or converted to a <math>\text{C}_{1-4}</math> thioalkyl ether thereof by reaction with sodium alkoxide and an alkyl halide). In the second step, mesna is oxidised <i>in situ</i> with oxygen gas to yield dimesna. Higher alkane homologues and analogous phosphonates are prepared similarly. When preparing a phosphonate analogue a haloalkanephosphonate is an alternative starting compound. The <math>\text{C}_{1-4}</math>-alkylene chain analogues of these compounds can be prepared similarly.</p> |           |   |

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PROCESS FOR PRODUCING MERCAPTOALKANESULFONATES  
AND PHOSPHONATES AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

This invention relates to a process for producing  
5 mercaptoalkanesulfonates and phosphonates and derivatives  
thereof, especially sodium 2-mercaptoethanesulfonate  
(mesna;  $\text{HS-CH}_2\text{CH}_2\text{SO}_3\text{Na}$ ) and disodium 2,2'-  
(dithiobis)ethane sulfonate (dimesna;  $\text{NaSO}_3\text{CH}_2\text{CH}_2\text{-S-S-CH}_2\text{CH}_2\text{SO}_3\text{Na}$ ).

BACKGROUND OF THE INVENTION

10 Compounds of the general formula (I):  $\text{R}_1\text{-S-(CH}_2\text{)}_m\text{-R}_2$   
wherein  $\text{R}_1$  is hydrogen,  $\text{C}_{1-4}$ -alkyl or  $\text{R}_2\text{-(CH}_2\text{)}_m\text{-S-}$  and  $\text{R}_2$  is  
 $\text{SO}_3\text{M}$  or  $\text{PO}_3\text{M}_2$  wherein M or each M independently is sodium,  
potassium or hydrogen and m is 2, 3 or 4, are useful  
15 *inter alia* as chemotherapeutic protective agents used to  
mitigate the toxicity of platinum complex antitumor drugs  
which are given to patients with certain types of cancer.  
Thus, dimesna can be co-administered with cisplatin (cis-  
diamminedichloroplatinum) to protect the body against  
20 nephrotoxicity, and both mesna and dimesna can be co-  
administered with carboplatin (cisdiammine-1,1-  
cyclobutanedicarboxylatoplatinum) to protect the body  
against myelosuppression. Mesna has also been used as a  
protective agent with other antitumor drugs e.g.  
25 ifosfamide, oxazaphosphorine and etoposide.

Mesna is auto-oxidized in the body to dimesna under  
mildly basic conditions and in the presence of oxygen  
species, such as those present in plasma.

The chief prior processes for synthesizing mesna and  
30 dimesna (and like mercaptans and disulfides) include the  
conversion of various alkanesulfonic acids into their  
respective mercaptan derivatives (such as mesna) and the  
subsequent oxidation of the mercaptans into their  
respective disulfides (such as dimesna) by use of iodine-  
35 containing reagents, such as iodate. These processes,

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while efficient, required isolation procedures to be performed to isolate and purify the end products from the reagents used. These processes generated environmental pollutants, which required disposal and could not be carried out in a single reaction vessel.

## SUMMARY OF THE INVENTION

The present invention avoids these disadvantages in the production of dimesna and provides a more convenient method of making various alkylthio-, mercapto- and dithiobis-alkanesulfonates and phosphonates.

The invention provides a process of making compounds of the general formula I, said process comprising

(1) reacting a compound of formula



wherein

X and Y together complete an olefinic carbon-carbon double bond or, where  $\text{R}_2$  is  $\text{PO}_3\text{M}_2$ , X can be halo and Y is then hydrogen;

n is 0, 1 or 2; and

$\text{R}_2$  is as defined above, with a sulfide of the general formula  $\text{Z}-\text{SH}$ , wherein Z is hydrogen, sodium or potassium, and where  $\text{R}_2$  is  $\text{PO}_3\text{M}_2$  the reaction is carried out in the presence of a free radical initiator when X and Y together represent a double bond or with the aid of heat when X represents halo and Y is hydrogen;

to form a mercaptan of formula I wherein  $\text{R}_1$  is hydrogen, and then optionally:

(2) (a) heating the mercaptan produced in Step (1) with oxygen gas, under pressure, to produce a compound of formula I wherein  $\text{R}_1$  is  $\text{R}_2-(\text{CH}_2)_n-\text{S}-$  or

(b) reacting the mercaptan produced in Step (1) first with a  $\text{C}_{1-4}$  alkali metal alkoxide in a protic solvent and then with an alkyl bromide or iodide, to produce a compound of formula I wherein  $\text{R}_1$  is  $\text{C}_{1-4}$ -alkyl.

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The process is summarised by the following chart:



or



(n = 0, 1 or 2, R<sub>2</sub> = PO<sub>3</sub>M<sub>2</sub>

or SO<sub>3</sub>M, M = Na, K or H)

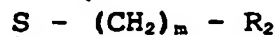
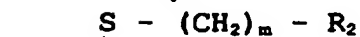
H<sub>2</sub>S or NaHS

(Step 1)



O<sub>2</sub>  
(Step 2a)

C<sub>1-4</sub> - alkoxide,  
Protic solvent,  
Hal - C<sub>1-4</sub> - alkyl  
(Step 2b)



(m = n + 2)

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred process of this invention for preparing the compounds of formula I wherein R<sub>1</sub> is R<sub>2</sub>-(CH<sub>2</sub>)<sub>m</sub>-S- involves two-steps in a single-pot, which results in the conversion of an alkenyl sulfonate salt or acid (ω-alkenesulfonate or -sulfonic acid) to the desired formula I compound, especially dimesna which can be produced thereby in a highly pure form, on a large scale.

Step 1 involves the addition of a sulfhydryl moiety in an anti-Markovnikov fashion to the unsaturated terminal double bond by generating an sp<sup>3</sup> center. The addition to the double bond is effected by reacting the starting alkenyl sulfonate salt with a hydrosulfide salt or with hydrogen sulfide, preferably in a slightly basic

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solution (pH from 8 to 9.5). The sulfide is preferably present in at least a stoichiometric proportion and usually in a molar excess of at least 2:1, preferably from 3:1 to 5:1. This step forms a mercapto-  
5 (alternatively termed a sulfhydryl-) alkanesulfonate which may be recrystallized directly to produce the compounds of formula I wherein R<sub>2</sub> is hydrogen, especially mesna.

Step 2 of this process, designated step 2(a) above,  
10 involves the oxidization of the mercaptoalkanesulfonate to a disulfide and is performed in an aqueous medium and in the same reaction vessel as step 1, without the need to purify or isolate the product of step 1. Step 2 includes the introduction of oxygen gas, preferably by  
15 bubbling, into the reaction vessel, along with an increase in pressure and temperature above ambient values, preferably at a slightly basic pH. The preferred pH is from 8 to 9.5. It can remain unadjusted from step 1 which is a big advantage. The preferred temperature is  
20 at least 40°, most preferably at least 60°C. A range of 40 to 100°C is contemplated for most purposes. The preferred gauge (superatmospheric) pressure is at least 20psi (138 kPa), more preferably at least 30psi (207 kPa) and most desirably at least 50psi (345kPa). A range of  
25 20 to 60psi (138 to 414kPa) is contemplated for most purposes. Dimesna or a homologue or analogue thereof can be formed in substantially quantitative yield. The desired final product can be easily crystallized from the aqueous reaction medium itself.

30 If the desired end product is an alkyl thioether of formula I wherein R<sub>1</sub> is C<sub>1-4</sub> alkyl, step 1 of the process is performed as described above and the mercaptan product is then taken up in a protic solvent, preferably a C<sub>1-4</sub>-alkanol, which contains a desired C<sub>1-4</sub>-alkoxide,  
35 preferably sodium methoxide. Preferably, the solution is

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warmed to about 60°C, followed by the addition of the C<sub>1-4</sub> alkyl iodide or bromide to effect the alkylation. Preferably the alkyl portion of the alkoxide is the same as that of the alkyl iodide or bromide and even more preferably the protic solvent comprises the corresponding alkanol. The thioether is thus formed in generally quantitative yield.

When a phosphonate of formula I is desired, the starting compound can be a haloalkanephosphonate, preferably a bromoalkane- or chloroalkanephosphonate. Preferably n is 0 or 1, the starting material then being a haloethane- or halopropanephosphonate. The two step, single pot process involves first the treatment of this starting compound with sodium hydrosulfide or hydrogen sulfide at elevated temperature, especially from 40 to 120°. The sulfide is preferably used in molar excess, as described above. Alternatively, step 1 may be achieved by converting the alkenephosphonic acid to the mercaptan by addition of a sulfur source, conditions and reagents being as described above, in the presence of a free radical initiator. Step 2, the oxidation to the disulfide, is the same as described above.

The following non-limiting examples illustrate the invention.

25

## EXAMPLE 1

## Disodium 2,2'-(dithiobis)ethanesulfonate

100mL of a 25% aqueous stock solution (25 grams VSA, 0.192 mole) of vinylsulfonic acid (VSA) sodium salt (Aldrich Chemical Company) was taken up in a Parr vessel, and argon gas bubbled in for one hour to deoxygenate the aqueous solution. To this solution was added 33.5 grams (0.598 mole, reckoned as NaSH) of sodium hydrosulfide monohydrate (Aldrich Chemical Company) and 10mL of sodium hydroxide. The pH of the solution was approximately 9.0. The reaction mixture was agitated in a Parr apparatus

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for two hours, during which time NMR monitoring was conducted at 30 minute intervals.

The product obtained from this step was taken to the next step without isolation, heated to 60°C, and oxygen  
5 bubbled into the vessel for thirty minutes. The vessel was then pressurized to 50psi (345kPa) gauge and agitated for six more hours at 60°C.

The completed reaction mixture was then worked up by concentrating the aqueous fraction at 80°C using an  
10 industrial vacuum, followed by diffused recrystallization from water. The crystallized product was then lyophilized after adjusting the pH to 7.2 by adding 1N HCl and filtering through a 0.2 micrometre pore membrane filter. NMR and elemental analysis confirmed the  
15 presence of pure (99%) sodium 2,2'-(dithiobis)ethanesulfonate.

#### EXAMPLE 2

##### Tetrasodium 2,2'-(dithiobis)ethanephosphonate

2-Chloroethanephosphonic acid (1 gram; 6.9 mmoles)  
20 was taken up in anhydrous ethanol (10ml) and degassed with a continuous stream of argon for at least 30 minutes. This was then added to a boiling solution of sodium hydrosulfide hydrate (1.4 g, 25 mmol, reckoned as NaSH) in ethanol to obtain a reaction mixture with a  
25 final pH of approximately 9. The resultant reaction mixture was then refluxed for 10 hours. The reaction mixture was then cooled and the pH adjusted to 8 using 1N HCl. The solvent was removed and the product was purified by diffused crystallization. The white solid  
30 was then taken into a Parr bottle and 50 ml water added. The aqueous solution was then bubbled with a stream of oxygen for a period of at least one hour. Then the bottle was pressurized with 50psi (345kPa) gauge oxygen and shaken at 60°C for 4 hours. The product was isolated



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by concentrating the aqueous portion to half at 80°C under industrial vacuum, followed by crystallization. The product thus obtained was then characterized by high field NMR and elemental analysis and by comparing with an authentic sample.

## EXAMPLE 3

## Tetrasodium 2,2'-(dithiobis)ethanephosphonate

Example 2 was repeated except that the same molar amount of 2-bromoethanephosphonic acid was used as the starting material and the ethanol solvent replaced by water. The title compound thus obtained was then characterized by high field NMR and elemental analysis and by comparing with an authentic sample.

## EXAMPLE 4

## Monosodium 2-(methylthio)ethanesulfonate

Sodium methoxide (1.5 gram) was taken up in anhydrous methanol (20 ml) and sodium mercaptoethanesulfonate (mesna) (1g) added. The reaction mixture was then refluxed for 6 hours. To the above solution was then added methyl iodide (2ml) and the solution stirred for an additional 2 hours. The reaction mixture was then concentrated and the product was crystallized from water. The title compound, obtained in quantitative yield, was characterized by NMR:

$^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ): 1.99 $\delta$  (3H, s); 2.67-2.72 $\delta$  (2H, m); 2.99-3.04 $\delta$  (2H, m)

$^{13}\text{C}$  NMR:  $\delta$  13.89, 27.28, 29.92, 50.31

## EXAMPLE 5

## Monosodium 2-(ethylthio)ethanesulfonate

Example 4 was repeated, substituting the same weights and volumes of sodium ethoxide, ethanol and ethyl iodide for sodium methoxide, methanol and methyl iodide.

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The title compound, obtained in quantitative yield, was characterized by NMR:

$^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ): 1.07 $\delta$  (3H, t,  $J= 7.5\text{Hz}$ );

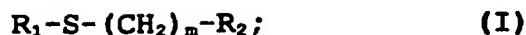
5 2.45 $\delta$  (2H, q,  $J= 7.5\text{ Hz}$ ); 2.69-2.75 $\delta$  (2H, m); 2.96-3.02 $\delta$   
(2H, m)

$^{13}\text{C}$  NMR:  $\delta$  12.65, 23.84, 24.05, 28.96, 49.98

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## CLAIMS

1. A process for producing compounds of the general formula:



5 wherein

$R_1$  is hydrogen,  $C_{1-4}$ -alkyl or  $R_2-(CH_2)_m-S-$ ;

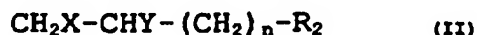
$R_2$  is  $SO_3M$  or  $PO_3M_2$  wherein  $M$  or each  $M$  independently is sodium, potassium or hydrogen,

and

10  $m$  is 2, 3 or 4,

said process comprising

(1) reacting a compound of formula



wherein

15  $X$  and  $Y$  together complete an olefinic carbon-carbon double bond or, where  $R_2$  is  $PO_3M_2$ ,  $X$  can be

halo and  $Y$  is then hydrogen;

$n$  is 0, 1 or 2; and

$R_2$  is as defined above,

20 with a sulfide of the general formula  $Z-SH$ , wherein  $Z$  is hydrogen, sodium or potassium, and where  $R_2$  is  $PO_3M_2$  the reaction is carried out in the presence of a free radical initiator when  $X$  and  $Y$  together represent a double bond or with the aid of heat when  $X$  represents halo and  $Y$  is  
25 hydrogen;

to form a mercaptan of formula I where  $R_1$  is hydrogen, and optionally:

(2) (a) heating the mercaptan produced in step (1) with oxygen gas under pressure, to produce a compound of  
30 formula I wherein  $R_1$  is  $R_2-(CH_2)_m-S-$  or

(b) reacting the mercaptan produced in step (1) first with a  $C_{1-4}$  alkali metal alkoxide in a protic solvent and then with an alkyl bromide or iodide, to produce a compound of formula I wherein  $R_1$  is  $C_{1-4}$ -alkyl.

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2. A process according to Claim 1, wherein in step (1) the molar ratio of sulfide to compound of formula (2) is in excess of stoichiometric.
3. A process according to Claim 1 or 2, wherein in step  
5 (2)(a) the pressure is at least 20psi (138kPa) gauge and the reaction is carried out at a temperature of at least 60°C.
4. A process according to Claim 3, wherein in step (2)(a) the pressure is at least 30psi (207kPa) gauge.
- 10 5. A process according to Claim 1, 2, 3 or 4, wherein step (2)(a) is carried out to produce a compound of formula I wherein  $R_1$  is  $MSO_3-(CH_2)_2-S-$ .
6. A process according to Claim 5, wherein the starting compound is a vinyl sulfonate of formula II wherein X and  
15 Y together form a double bond, n is 0 and  $R_2$  is  $SO_3M$ , the mercaptan reaction product of step (1) is not isolated and step (2)(a) is carried out in the same reaction vessel as for step (1).
7. A process according to Claim 5 or 6, wherein M is  
20 sodium and the product is dimesna.
8. A process according to Claim 1, 2, 3 or 4, wherein in step (2)(b) the protic solvent is a  $C_{1-4}$  alkanol and the  $C_{1-4}$  alkyl moiety of the alkoxide, the alkyl bromide or iodide and the alkanol is the same.
- 25 9. A process according to Claim 1, 2, 3, 4 or 8, wherein in step (2)(b) the  $C_{1-4}$ -alkyl bromide or iodide is methyl or ethyl bromide or iodide.

# INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/GB 97/02576

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C319/04 C07C319/14 C07C319/24 C07C323/66 C07F9/38

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## B. FIELDS SEARCHED

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages            | Relevant to claim No. |
|------------|---|-----------------------|
| A          | US 3 639 430 A (H. ALTERMATT) 1 February 1972<br>see column 17, line 50 - line 51<br>---      | 1                     |
| A          | US 5 347 015 A (H. KELLER, ET AL.) 13 September 1994<br>see the whole document<br>---<br>-/-- | 1                     |



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Patent family members are listed in annex.

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Date of the actual completion of the international search

12 December 1997

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
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| A        | CHEMICAL ABSTRACTS, vol. 108, no. 22,<br>30 May 1988<br>Columbus, Ohio, US;<br>abstract no. 193285b,<br>H. LEE, ET AL.: "Adsorption of ordered<br>zirconium phosphonate multilayer films on<br>silicon and gold surfaces"<br>page 432;<br>XP002050051<br>see abstract<br>&<br>JOURNAL OF PHYSICAL CHEMISTRY,<br>vol. 92, no. 9, 1988,<br>pages 2597-2601,<br>----   | 1                     |
| A        | CHEMICAL ABSTRACTS, vol. 110, no. 3,<br>16 January 1989<br>Columbus, Ohio, US;<br>abstract no. 23982a,<br>J.T. DOI, ET AL.: "Neighbouring group<br>participation in organic redox reactions.<br>13. Intramolecular interaction of the<br>beta-phosphonic acid group in the aqueous<br>iodine oxidation of thio ethers and<br>disulphides. Generation of a<br>phosphonic-phosphoric anhydride"<br>page 563;<br>XP002050052<br>see abstract<br>&<br>PHOSPHORUS SULFUR,<br>vol. 35, no. 1-2, 1988,<br>pages 173-182,<br>---- | 1                     |
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# INTERNATIONAL SEARCH REPORT

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In ternational Application No

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| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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